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Extra View

Iron toxicity

New conditions continue to emerge

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Abbreviations: ALS, amyotrophic lateral sclerosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PAP, pulmonary alveolar proteinosis; PKAN, pantothenate kinase-associated neurodegeneration

Key words: aging muscle atrophy, iron, iron associated diseases, iron toxicity, pulmonary alveolar proteinosis, rosacea, viral replication

During the past half century, excessive/misplaced iron has been observed to be a risk factor for an increasing number and diversity of disease conditions. An extensive list of conditions and of the types of iron association were published in early 2008. Within the subsequent year, four additional disorders have been recognized to be enhanced by iron: aging muscle atrophy, viral replication, rosacea and pulmonary alveolar proteinosis. This paper adds new data and emphasis on these disorders as entities associated with increased iron load and toxicity.

A review written early in 2008 contained an extensive list of diseases for which excessive and/or misplaced iron has been reported to be a causative or associated risk factor.[1] The metal is toxic by catalyzing generation of hydroxyl radicals that intensify oxidative stress as well as by serving as a growth-essential nutrient for invading microbial and neoplasmic cells.

In the subsequent twelve months following submission of the manuscript, four additional conditions in which iron is toxic have been described: (a) intensification of aging muscle atrophy,[2] (b) increased replication of human immunodeficiency virus (HIV) and hepatitis C virus (HCV),[3] (c) enhancement of rosacea,[4] and (d) augmentation of pulmonary alveolar proteinosis (PAP).[5] In this paper, the previously published tables of iron-related conditions and of the types of iron association are expanded to include these four conditions.

In the report on muscle atrophy, non-heme iron levels in gastrocnemius muscle in male rats increased by 233% between six and thirty months of age.[2] Abundance of mRNA transferrin receptor-1 decreased by 80%. In related research in the same laboratory, non-heme iron and RNA oxidation increased significantly with age in quadriceps-derived subsarcolemma mitochondria.[6] In a third related study, in rats between 29 and 37 months of age, non-heme iron in gastrocnemius muscle increased by 200% with an accompanying significant increase in oxidized RNA[7] These changes were associated with evidence of sarcopenia; that is, decreased muscle mass and grip.

Although iron is not a component of viruses, infected host cells apparently need the metal to synthesize viral particles. During the past several decades, it has become manifest that one of the dangers of excessive iron is its ability to favor animal viral infections.[8] The importance of iron in HIV infection has received particular attention.[9] The multi-faceted molecular sites of action of iron in synthesis of HIV, as well as of HCV, are now being compiled.[3] Of special interest are indications that viruses can manipulate iron homeostasis so as to ensure their replication in host cells.

Rosacea is a common chronic light-sensitive inflammatory skin disease. In this inquiry, peroxide and antioxidant potential of serum as well as of skin cell ferritin were assayed.[4] Serum peroxide levels were higher and total anti-oxidant potential was lower in patients than in healthy controls ($p < 0.05$). The number of ferritin positive cells was higher ($p < 0.001$) in patient samples especially in those with severe disease. Ultraviolet irradiation of skin plus skin cell iron accelerated development of photo-sensitization, photo-aging and skin cancer.[10] It will be of interest to directly measure iron deposits in rosacea cells.

In the investigation on PAP, bronchoalveolar lavage samples of 20 patients were compared with those of 20 healthy volunteers.[5] Concentrations of iron, transferrin, transferrin receptor, lactoferrin and ferritin were significantly elevated in PAP relative to healthy persons. In contrast, quantities of ascorbate, glutathione and urate were significantly depressed in PAP patients, indicative of anti-oxidant depletion. The results suggest an iron-catalyzed oxidative stress in the maintenance of PAP.

Similar alterations in pulmonary iron homeostasis have been observed in several other chronic lung diseases.[11]

The list of iron-associated diseases, whose compilation began 25 years ago,[12] continues to grow (Tables 1 and 2). Recognition of the toxicity of iron is stimulating research efforts to develop iron chelator drugs that might be able to remove the metal from specific disease sites.[13,14]

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Table 1 **Conditions for which excessive/misplaced iron can be a risk factor**

Aging	**Infectious**	**Ophthalmic**
muscle atrophy	bacterial, fungal & protozoan infections	macular degeneration
Cardiovascular	viral infections: HIV, HCV	**Orthopedic**
atherosclerosis		gout
cardiomyopathy	**Neurologic**	hemophilic
hypertension	ALS	synovitis
ischemic stroke	Alzheimer	osteoarthritis
venous leg ulcer	depression	osteoporosis
	Friedreich ataxia	
Dermal	Huntington	**Otologic**
porphyria	multiple sclerosis	aminoglycoside
cutanea tarda	Parkinson	toxicity
rosacea	PKAN	
	prion disease	**Pediatric & Neonatal**
Endocrine		Down syndrome
diabetes	**Obstetric**	epilepsy
endometriosis	neonatal	sudden infant death
growth deficiency	hemochromatosis	
hypogonadism	pre-eclampsia	**Pulmonary**
hypothyroidism		alveolar proteinosis
	Oncologic	cystic fibrosis
Hepatic	breast	ozone lung injury
cirrhosis	colorectal	pneumoconiosis
steatohepatitis	esophageal	**Renal**
viral hepatitis	hepatic	aminoglycoside &
	Kaposi sarcoma	vancomycin toxicity
	leukemia	
	lung	

Modifed from Table 3 (Weinberg et al.)[1].

Table 2 **Association of iron with morbidity**

- **Iron, by itself, has been observed to initiate the disease**
  - cardiomyopathy
  - growth deficiency
  - hemophilic synovitis
  - hypogonadism
  - lung cancer
  - osteoporosis
  - pneumoconiosis
- **Iron can be a cofactor in promoting the disease**
  - Alzheimer
  - atherosclerosis
  - bacterial infections
  - diabetes
  - endometriosis
  - esophageal adenocarcinoma
  - fungal & protozoan infections
  - gout
  - hepatoma
  - multiple sclerosis
  - osteoarthritis
  - oto- & renal toxicity
  - ozone lung injury
  - pulmonary alveolar proteinosis
  - viral infections
- **Iron deposits are observed in disease-associated tissue sites**
  - basal ganglia in PKAN
  - hepatocytes in cirrhosis, steatohepatitis & viral hepatitis
  - mitochondria in Friedreich ataxia
  - pulmonary secretions in cystic fibrosis
  - retina in macular degeneration
  - skin cells in rosacea
  - skeletal muscle in aging
  - substantia nigra in Parkinson
  - thyroid in hypothyroidism
- **Body iron loading is associated with above normal incidence of morbidity**
  - ALS
  - breast cancer
  - colorectal cancer
  - depression
  - Down syndrome
  - epilepsy
  - hypertension
  - ischemic stroke
  - leukemia
  - pre-eclampsia
  - porphryia cutanea tarda
  - prion disease
  - sudden infant death syndrome
- **Maternal antibodies can impair fetal iron metabolism**
  - fetal or neonatal death in neonatal hemochromatosis

Modified from Table 4 (Weinberg et al.)[1].

References

1. Weinberg ED, Miklossy J. Iron withholding: A defense against disease. J Alz Dis 2008; 13:451-63.
2. Hofer T, Marzetti E, Xu J, Seo AY, Gulec S, Knutson MD, et al. Increased iron content and RNA oxidative damage in skeletal muscle with aging and disease atrophy. Exp Geront 2008; 43:563-70.
3. Drakesmith H, Prentice A. Viral infection and iron metabolism. Nat Rev Microbiol 2008; 6:541-55.
4. Tisma VS, Basta-Juzbasic A, Jaganjac M, Brcic L, Dobric I, Lipozencic J, et al. Oxidative stress and ferritin expresson in the skin of patients with rosacea. J Am Acad Dermatol 2009; 60:270-6.
5. Ghio AJ, Stoneheurner JG, Richards JH, Crissman KM, Roggli VL, Plantadosi CA, et al. Iron homeostasis and oxidative stress in idiopathic pulmonaryalveolar proteinosis. Respir Res 2008; 9:10.
6. Seo AY, Xu J, Servais S, Hofer T, Marzetti E, Wohlgemuth SE, et al. Mitochondial iron accumulation with age and functional consequences. Aging Cell 2008; 7:706-16.
7. Xu J, Knutson MD, Carter CS, Leeuwenburgh C. Iron accumulation with age, oxidative stress and functional decline. PLoS ONE 2008; 3:e2865.
8. Weinberg ED. Iron withholding: A defense against viral infections. BioMetals 1999; 9:393-9.
9. Weinberg GA, Boelaert JR, Weinberg ED. Iron and HIV infection. In Friis H, ed. Micronutrients and HIV Infection. CRC Press Boca Raton, FL 135-58.
10. Kitazawa M, Iwasaki K. Reduction of ultraviolet light-induced oxidative stress by amino acid chelators. Biochim BiophysActa 1999; 1473:400-8.

11. Ghio AJ. Disruption of iron homeostasis and lung disease. Biochim Biophys Acta (General Subjects) 2008; e-pub.
12. Weinberg ED. Iron withholding: A defense against infection and neoplasia. Physiol Rev 1984; 64:65-102.
13. Tam TF, Leung-Toung R, Li W, Wang Y, Karimian K, Spino M. Iron chelator research: Past, present, future. Curr Medicinal Chem 2003; 10:983-95.
14. Hider RC, Ma Y, Molina-Holgado F, Gaeta A, Roy S. Iron chelation as a potential therapy for neurodegenerative disease. Biochem Soc Trans 2008; 36:1304-8.